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# Risk of Serotonin Syndrome with Isoniazid

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Latent *Mycobacterium tuberculosis* infections causing tuberculosis (TB) are estimated to affect a quarter of the world's population (1), leading to 10 million TB cases and 1.2 million TB-related deaths in 2018 (2). Treatment of latent TB infection is often isoniazid or rifampin. Though rifampin is preferred due to a shorter course of therapy (3), its numerous drug interactions can limit its use. Isoniazid is typically thought to have fewer potential drug interactions. However, isoniazid does possess some monoamine oxidase (MAO) inhibitor activity, though this is not usually of clinical significance as it is quite weak (4). Unfortunately, the interaction does not generate a flag in most drug interaction checkers, increasing the risk of serotonin syndrome if a patient is prescribed multiple serotonergic agents.

Mirtazapine is a tetracyclic antidepressant which is thought to lead to increased activity of noradrenaline and serotonin (5). When taken in supratherapeutic doses, mirtazapine does not appear to cause serotonin syndrome by itself but conditions consistent with serotonin syndrome have been reported when mirtazapine is ingested with additional serotonergic agents (6–8).

Here, we present a case of suspected serotonin syndrome, secondary to concomitant use of isoniazid and mirtazapine.

A 35-year-old woman with a past medical history of depression on mirtazapine 15 mg nightly and with alcoholic hepatitis underwent liver transplantation at an outside hospital. Her living donor was known to have latent tuberculosis. Following transplant, she was started on isoniazid 300 mg daily and pyridoxine 25 mg daily for tuberculosis prophylaxis, per guidelines (9). Rifampin was avoided given its significant drug interactions with her transplant-related medications.

Six days following the initiation of isoniazid, the patient's spouse reported that she was not at her baseline mental status. At her outpatient infectious diseases clinic visit, she was found to be oriented to herself only and was unable to stand or walk. Due to the severity of her symptoms, she was admitted to the hospital and underwent emergent computed tomography (CT) and magnetic resonance imaging (MRI) of the head, which were negative for any intracranial abnormality. The patient had also developed new diarrhea, nausea, tremors, hypertension, and altered mental status since starting isoniazid. Her renal and hepatic functions were near her baseline at the initiation of isoniazid as well as on the day of presentation, with serum creatinine 1.09 mg/dl, alanine aminotransferase (ALT) 24 U/liter, aspartate aminotransferase (AST) 131 U/liter, total bilirubin 0.9 mg/dl, and prothrombin time/international normalized ratio (PT-INR) 1.2. Given these symptoms and the time course, and after consultation with psychiatry, the patient was given the presumptive diagnosis of serotonin syndrome. The isoniazid and mirtazapine were held, the patient's symptoms slowly dissipated, and she was ultimately discharged home symptom-free.

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Our case of presumed serotonin syndrome provides an opportunity to educate clinicians on the potential risk of serotonin syndrome associated with the use of isoniazid in combination with mirtazapine. Though the patient did not meet the Hunter criteria for diagnosis of serotonin syndrome, she did possess the appropriate symptoms to be given the diagnosis via the Sternbach criteria (10). We hope this case can improve provider awareness of MAO inhibition of isoniazid and help avoid potential harm, since the MAO inhibition activity of isoniazid is not frequently identified via interaction checking software. However, given the relative rarity of such an adverse reaction, we recommend only increased monitoring and early intervention for patients with suspected serotonin syndrome secondary to isoniazid, so as to not limit the use of isoniazid.

We present a case of suspected serotonin syndrome in a patient on isoniazid and mirtazapine. Isoniazid possesses weak MAO inhibition, which may contribute to serotonin syndrome when used in combination with other serotonergic medications.

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